Original Research

Low serum triiodothyronine and potassium levels are associated with increased risk of eclampsia among women in the Eastern Cape Province of South Africa

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Abstract

Background: There is paucity of data on the relationship between thyroid hormones, potassium and eclampsia. Moderate-to-severe iodine deficiency that worsens during pregnancy leads to decreased thyroid hormone output and bioavailability to the brain. Apart from metabolic functions, T3 and T4 are essential fast acting cytosolic and synaptosomal neural transmitters that also regulate neuronal excitatory-inhibitory mechanisms. T3 also regulates the Na^+-K^+-ATPase pump that maintains the membrane ionic gradient. Hence altered serum potassium, thyroxine and triiodothyronine levels could increase the risk of eclamptic seizures. **Methods**: Forty-five women with eclampsia, 45 severe preeclampsia and 90 normotensive pregnant controls were enrolled into this study. Levels of thyroid hormones, thyroglobulin and urine iodine concentration (UIC) were measured and compared between the three groups. **Results**: Eclamptic participants had significantly lower median serum potassium (K), triiodothyronine (FT3), urinary iodine concentration (UIC) but higher serum thyroglobulin (Tg) (K = 3.7 mmol/L; FT3 = 3.8 pmol/L; UIC = 69.5 μg/L; Tg = 39.0 μg/L) than normotensive pregnant controls (K = 4.3 mmol/L; T3 = 4.7 pmol/L; UIC = 169.5 μg/L; Tg = 19.5 μg/L) and participants with severe preeclampsia (K = 4.2 mmol/L; T3 = 4.4 pmol/L; UIC = 95.7 μg/L; Tg = 22.4 μg/L), $p < 0.05$. Low UIC, low serum T3 and potassium and elevated Tg were independent predictors of eclampsia. **Conclusions**: Women with iodine deficiency in pregnancy may be at increased risk of eclampsia secondary to the ensuing rapid peripheral turnover of thyroid hormones leading to hypothyroxinaemia and reduced triiodothyronine bioavailability to the central nervous system that can be exacerbated by hypokalaemia.

Keywords: Low serum triiodothyronine; Low serum potassium; Pregnancy; Eclampsia

1. Background

Although preeclampsia complicates 5–10% of all pregnancies worldwide, eclampsia, one of the most severe complications of preeclampsia, is associated with 8-fold maternal mortality compared to preeclampsia [1,2]. Thyroid dysfunction, iodine and potassium deficiency in pregnancy have all been associated with preeclampsia [3–6]. However, there is paucity of data on the thyroid function status, iodine nutrition status, as well as the serum potassium levels of women with eclampsia. The pathways through which iodine and potassium deficiency as well as thyroid dysfunction may interact to increase the risk of eclampsia have not yet been described.

The thyroid gland responds to iodine deficiency by preferential secretion of triiodothyronine (T3) instead of T4 leading to low serum thyroxine (T4) [7]. However, only a minute amount of T3 is directly transported from the blood stream to the central nervous system (CNS). The brain derives most of its T3 by deiodination of T4 by type 2 deiodinase (D2) [8,9]. Apart from regulation of metabolism,

T3 and T4 are essential in the central nervous system for modulation of fast acting cytosolic physiological action and neurotransmitter activity at synaptic junctions [8,9]. T3 also regulates the Na^+-K^+-ATPase pump that maintains the membrane ionic gradient of the neurones by pumping sodium out and potassium into the cells [8]. Hence among pregnant women with iodine deficiency, the preferential production of T3 could result into low serum T4 leading to T3 deficiency in the central nervous system (CNS). This could adversely affect the synaptosomal neurotransmitter function of T3 and the stability of the cell membrane ionic gradients potentially increasing the risk of eclampsia.

The pathophysiology of eclampsia is yet to be fully understood. It is still not yet certain why eclampsia complicates both women with mild and severe hypertension in pregnancy. We carried out this case-control study to compare the serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and potassium of women with eclampsia, preeclampsia with severe features (from now onwards termed as 'severe

preeclampsia') and normotensive pregnant controls; and to ascertain if serum T3, T4 and potassium levels were associated with the risk of eclampsia.

2. Materials and methods

This prospective case control study enrolled eligible participants who received maternity care from Nelson Mandela Academic Hospital, Mthatha and Mthatha Regional Hospital between August 2018 and March 2020. Forty-five women with eclampsia referred to Nelson Mandela Academic hospital were consecutively recruited into the study as cases. Forty-five women with severe preeclampsia and ninety counterparts who remained normotensive until delivery were randomly selected as controls. Participants with eclampsia and severe preeclampsia were diagnosed and managed according to International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines [10]. The patients with hypertensive disease in pregnancy are given methyldopa as the first line drug for the control of hypertension if they have mild hypertension, and nifedipine, hydralazine and labetalol as recommended by the ISSHP for those with severe hypertension. Once the blood pressure is within the range of 110–140/85 mmHg they are we maintained on methyldopa alone or in combination with oral hydralazine (Aspen Pharmacare, Durban, South Africa) and or Amlodipine (Accord Health Care, North Harrow, United Kingdom) when necessary. Magnesium sulphate is administered according to the guidelines ISSHP for the prevention and attenuation of eclamptic seizures.

The levels of TSH, FT4 and FT3 were determined using electrochemiluminescence immunoassay (Roche/Hitachi cobas c systems). Serum obtained by centrifuging venous blood samples was aliquoted and stored at –20 °C until analysis for thyroid function tests (TSH, T4, T3, and thyroglobulin) at the Mthatha National Laboratories Services (NHLS) Chemical Pathology Laboratory. Urinary Iodine concentrations was determined from urine samples stored at –20 °C using the inductively coupled plasma (ICP) Mass Spectrometry method according to the manufacturer's instructions (Quadrupole Inductively Coupled Plasma Mass Spectrometry (X-Series 2 ICP-MS—Thermo-Fisher Scientific, Bremen, Germany)).

3. Statistical analysis

Data analysis was performed using software package IBM SPSS STATISTICS version 22 for Windows (IBM Inc., Chicago, IL, USA). We used the Shapiro–Wilk's test to check if the data followed the normal distribution. The data are summarized as proportions (%) for categorical variables, means $\pm$ standard deviation (SD) for normally distributed, and as median (p25, p75) for non-normally distributed continuous variables, respectively. The Chi-square test was used to compare the distribution of categorical variables by status for hypertensive disease in pregnancy. The Kruskall-Wallis test, ANOVA and equivalents were used

as appropriate for continuous variable comparisons across groups. Univariable and multivariable logistic regressions were used to investigate the correlates of eclampsia. A p-value < 0.05 was considered significant.

4. Results

The median chronological age was 23 years for normotensive pregnant women, 23 years for women with severe preeclampsia and 18 years for eclamptic women. Eclamptic participants had lower median BMI (25.6 kg/m^2) compared to women with severe preeclampsia (27.2 kg/m^2) and normotensive pregnant women (28.1 kg/m^2) $p < 0.05$ (Table 1). The median gestational age at delivery was lower for women with eclampsia (34 WOA) and severe preeclampsia (33 WOA) than for normotensive pregnant counterparts (38 WOA) $p < 0.001$.

As expected, the median systolic BP (137.0 and 143.0 mmHg) and diastolic BP (88.0 and 95.0 mmHg respectively) of eclamptic and severe preeclampsia participants were higher than that of normotensive counterparts (systolic BP 123.0 and diastolic BP 76 mmHg, both $p < 0.001$). Eclamptic participants had significantly lower median UIC, FT3 and serum potassium but higher median thyroglobulin ($p < 0.05$) than normotensive and severe preeclamptic controls. Eclamptic participants had a lower median TSH than severe preeclampsia controls (1.9 vs 3.0 IU/L, $p > 0.05$, Table 1).

5. Correlates of eclampsia

Using normotensive pregnant women as the reference group, age below 20 years, primigravida status, BMI >30 kg/m^2, UIC $\leq$100 μg/L, FT3 <4.3 pmol/L, thyroglobulin $\geq$20 μg/L and K$^+$ <3.3 mmol/L were significantly associated with eclampsia in univariable analyses. However, only primigravida status, UIC $\leq$100 μg/L, FT3 <4.3 pmol/L, thyroglobulin $\geq$20 μg/L and K$^+$ <3.3 mmol/L remained significantly associated with eclampsia in a multivariable logistic regression model that included all the 9 variables (Table 2).

6. Discussion

The current study found that participants with eclampsia had significantly lower median UIC, FT3, serum potassium but higher median thyroglobulin than both normotensive and severe preeclampsia participants. This suggests iodine deficiency as the possible underlying cause of the low thyroid hormone output among eclamptic women. Secondly, primigravida status, low urinary iodine concentration, low serum FT3, low serum potassium and high serum thyroglobulin were independently associated with eclampsia. Women with eclampsia and severe preeclampsia had lower FT4 than normotensive counterparts. The main difference between women with eclampsia and severe preeclampsia was that participants with severe preeclamp-

Table 1. Comparative profile of women by status of hypertension in pregnancy.

Variable	Normotensive (n = 90) Median (p25, p75)	Severe preeclampsia (n = 45) Median (p25, p75)	Eclampsia (n = 45) Median (p25, p75)	p value
Age years	23.0 (20.0, 29.0)	23.0 (18.0, 29.0)	18.0 (17.0, 21.0)	<0.001
Gravidity	2.0 (1.0, 2.0)	1.0 (1.0, 3.0)	1.0 (1.0, 1.0)	0.001
GA at booking (WOA)	21.5 (18.0, 24.0)	20.0 (18.0, 23.0)	22.0 (17.5, 26.0)	0.601
GA at delivery (WOA)	39.0 (37, 40)	33.5 (30.0, 37.0)	34.0 (32.0, 38.0)	<0.001
BMI (kg/m^2)	27.9 (25.9, 31.6)	28.1 (24.9, 34.5)	25.6 (22.5, 28.7)	0.002
SBP mmHg	121.5 (114.0, 127.3)	143.0 (131.0, 151.0)	137.0 (125.5, 150.0)	<0.001
DBP mmHg	77.0 (70.0, 82.0)	95.0 (85.3, 99.8)	88.0 (73.0, 96.5)	<0.001
K$^+$ mmol/L	4.3 (3.9, 4.7)	4.2 (3.8, 4.7)	3.7 (3.2, 4.1)	<0.001
Creatinine mmol/L	55.5 (44.0, 62.0)	60.0 (48.5, 78.5)	72.5 (58.0, 85.5)	<0.001
HDL mmol/L	1.7 (1.3, 2.0)	1.9 (1.7, 2.7)	2.1 (1.5, 2.5)	0.002
LDL mmol/L	1.2 (0.82, 2.1)	1.4 (1.1, 1.6)	1.4 (1.1, 1.7)	0.349
TSH IU/L	2.3 (1.8, 3.0)	3.0 (2.1, 3.1)	1.9 (1.3, 3.4)	0.001
FT4 pmol//L	14.0 (12.4, 16.0)	12.9 (11.2, 14.6)	13.2 (11.5, 14.9)	0.010
FT3 pmol//L	4.7 (4.2, 5.1)	4.4 (3.7, 4.8)	3.8 (3.1, 4.2)	<0.001
Tg µg/L	19.5 (13.0, 33.9)	22.4 (14.9, 38.5)	39.0 (27.1, 54.2)	<0.001
UIC µg/L	169.5 (89.1, 288.9)	95.7 (53.2, 579.8)	69.5 (14.2, 238.1)	<0.001

Values, medians and 25th–75th percentiles.

BMI, Body mass index; DBP, diastolic blood pressure; GA, gestational age; HDL, high density lipoprotein; K$^+$, Serum Potassium; LDL, low density lipoprptein; TSH, Thyroid stimulating hormone; FT4, Thyroxine; FT3, Triidothyronine; Tg, Thyroglobulin; UIC, urine iodine concentration; SBP, systolic blood pressure.

Table 2. Univariable and multivariable odds ratios of the factors associated with eclampsia.

Variable	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age <20 yrs	4.90 (2.11–12.05)	<0.001	2.02 (0.45–9.17)	0.362
*Primigravida	5.05 (2.11–12.05)	<0.001	8.33 (1.34–52.63)	0.023
BMI >30 kg/m^2	3.58 (1.37–9.35)	0.009	2.39 (0.53–10.64)	0.254
TSH ≥3.0 IU/L	1.0 (0.46–2.16)	1.000	1.02 (0.29–3.66)	0.970
FT4 <12 pmol//L	2.36 (0.96–5.80)	0.060	2.34 (0.52–10.62)	0.269
*FT3 <4.3 pmol//L	6.67 (2.92–15.15)	<0.001	6.41 (1.80–22.73)	0.004
*Tg ≥20 µg/L	4.54 (1.74–11.81)	0.002	6.42 (1.23–32.80)	0.025
*UIC ≤100 µg/L	3.62 (1.61–8.13)	0.002	3.36 (1.02–11.00)	0.045
*K$^+$ <3.3 mmol/L	20 (4.27–90.91)	<0.001	32.25 (3.86–250.00)	0.001

BMI, Body mass index; K$^+$, Serum Potassium; TSH, Thyroid stimulating hormone; FT3, Triidothyronine; FT4, Thyroxine; Tg, Thyroglobulin; UIC, urine iodine concentration.

* $p < 0.05$.

sia had mild iodine deficiency, relative hypothyroxinaemia, and raised TSH but no significant reduction in T3 and serum potassium. Chasalow *et al.* [11] reported that some preeclamptic patients have low spiral steroids, a type of potassium sparing endogenous steroid. This observation deserves further investigation in our study population.

Previous studies have shown that persistent mild-to-moderate iodine deficiency with intact thyroid parenchyma is associated with preferential T3 secretion from the thyroid, lower serum T4 and raised serum thyroglobulin as observed in the current study among eclamptic respondents [12,13]. Low serum T4 is associated with reduced bioavail-

ability of T3 to brain tissue [12]. In adults, the CNS contains high concentration of thyroid hormones with the T3/T4 ratio higher than that in the serum [14]. The brain derives about 75% of T3 by deiodination of T4 [15,16]. The thyroid hormones (T3 and T4) not only stimulate metabolic functions through nuclear receptors with subsequent transcription and production of effector proteins [17], but also have been found to be cytosolic and synaptic neurotransmitters with the latter non-genomic action being relatively rapid compared to the genomically mediated metabolic function [18].

The results of the current study seem to suggest that women at risk of eclampsia may not only present with moderate iodine deficiency and lower serum FT4 than normotensive counterparts but could also be prone to rapid peripheral turnover of T3 that is not matched by adequate replacement from the thyroid gland [7]. Alternatively, there may be defective peripheral deiodination of FT4 with resultant generalised FT3 deficiency in serum, as well as in the central nervous system and other organs. This can occur due to selenium deficiency and other circumstances associated with inadequate function of the enzyme deiodinase 2 that is involved in peripheral conversion of FT4 to FT3 [19,20]. On the other hand, the pattern of thyroid function observed in the current study among women with severe preeclampsia is due to prolonged exposure to mild iodine deficiency in pregnancy, resultant thyroid adaptation with preferential T3 production and attenuated T4 negative feedback on the pituitary gland and resultant increase in TSH [7].

Early in the 20th century, use of large doses of thyroid extract was one of the interventions for the management and prevention of eclampsia [21]. However, the probable mode of action as well as the pathophysiology of preeclampsia and eclampsia was still elusive [21]. Given that the thyroid gland has iodine stores as well as T3 and T4 hormones, it was not stated which one or a combination of these compounds was of therapeutic value. It is now known that T4 and T3 stimulate fast and non-genomic effects in the central nervous system that are mediated through modulatory effect on Glutamate and GABA that respectively are the main excitatory and inhibitory neurotransmitters in the nervous system [22]. Glutamate binds to its ionotropic and metabotropic receptors eliciting excitatory postsynaptic potential and a cascade of intracellular reactions that are crucial for normal and balanced cognitive and motor function [22].

Both T3 and T4 potentiate glutamate excitatory postsynaptic responses mediated mainly through the ionotropic alphaamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and Kainate receptors [23]. However, it is only T3 that negatively modulates the glutamate postsynaptic response on the N-methyl-D-aspartate (NMDA) receptors, decreasing the excitability of post-synaptic neurone [24]. Therefore, low T3 may result in net motor neurone excitability resulting in the tonic-clonic seizures characteristic of eclampsia. The alteration in the physiological brain T3/T4 ratio has potential to alter normal neuronal function [25] and may partially explain the findings in the current study where women with eclampsia had lower FT3 and FT4 than women that remained normotensive until term.

The NMDA glutamate receptors, whose inhibitory effect is accentuated by T3, have high permeability for sodium and calcium ions that at resting membrane potential are blocked by magnesium ions [26]. Previous studies have found that magnesium sulphate attenuates eclamptic convulsions through blockage of these glutamate NMDA receptors [27]. Several authors have reported that women with eclampsia and preeclampsia had low serum magnesium [28–30]. These observations together with the finding of low FT3 as independent predictor of eclampsia in the current study seems to imply that low T3 potentiates the risk of eclamptic seizures among women with hypomagnesaemia through decreased inhibition of post-synaptic glutamate NMDA receptors.

GABA inhibitory responses are mediated via ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors [31]. Stimulation of post-synaptic $GABA_A$ receptors elicits transient large amplitude phasic inhibitory currents whose frequency and amplitude can be attenuated by both T3 and T4 [23]. Stimulation of extra-synaptic $GABA_A$ receptors stimulates lower amplitude but longer lasting tonic inhibitory currents that cause hyperpolarisation of the post-synaptic neurones [31–33] $GABA_B$ receptors on presynaptic membranes are sensitive to high concentration of GABA within the synaptic cleft hence inhibit further/excessive release of GABA from the synaptic vesicles [34]. Therefore, derangement in the physiological brain T3/T4 ratio may alter the GABA inhibitory responses with resultant clinical manifestations, one of which could be eclamptic seizures.

The stimulation of post-synaptic $GABA_B$ receptors results in activation of inward potassium channels and inhibition voltage gated sodium channels leading to hyperpolarization and increased action potential threshold [35]. In the current study, the observed association between low serum potassium and the increased risk of eclampsia may be secondary to the diminished effectiveness of this $GABA_B$ receptor mediated inhibition further predisposing pregnant women with low FT3 to the tonic-clonic convulsions that are characteristic of eclamptic fits.

The lower age and Body Mass Index for eclamptic participants compared to normotensive and women with severe preeclampsia in the current study may be accounted for by teenage pregnancy a known risk factor for eclampsia, which may predispose them to diet low on vegetables and fruits that are sources of potassium [36–38].

7. Study limitations

To our knowledge, this study is the first to report the possible role of combined triiodothyronine and potassium deficiency in the aetiology of eclampsia. Although median UIC at population level is good predictor of iodine intake, spot UIC is affected by considerable diurnal variation hence is not a reliable measure of iodine intake at individual level. However, serum thyroglobulin, a reliable measure of prolonged insufficient iodine intake, was significantly high among women with eclampsia suggesting that the observed thyroid dysfunction in the current study may be secondary to iodine deficiency. This also study is limited by the inability to determine serum magnesium levels before routine administration of prophylactic magnesium sulphate since magnesium deficiency is a potential confounder. The non-thyroidal illness syndrome (Euthyroid sick syndrome) is another potential confounder of the observed thyroid dysfunction attributed to iodine deficiency among participants with severe preeclampsia and eclampsia.

8. Conclusions

Low serum T4 and T3 may predispose to reduced bioavailability of T3 in the CNS and alteration in the physiological T3/T4 ratio. This may attenuate the inhibitory effects of GABA, while the excitatory function of glutamate remains intact, resulting in net motor neurone stimulation. This may predispose to the involuntary tonic-clonic convulsions observed in eclampsia. This may further be exacerbated by low serum potassium that attenuates $GABA_B$ receptor mediated tonic extra-synaptic inhibition and magnesium deficiency, which potentiates the NMDA receptor mediated activation of post-synaptic neurones.

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Author contributions

CBB conceived and designed the study, collected and analysed the data and wrote the first manuscript. APK and BLM carried out the critical review of the manuscript. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

We obtained ethical approval from Walter Sisulu University and the University of Cape Town Human Research Ethics Review Committees (reference number 066/2017 and 135/2018 respectively). All participants provided informed written consent before enrolment into the study.

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Conflict of interest

The authors declare no conflict of interest.

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